REMARKS

Claims 1-10, 24-40, 42-43, 49-60, 62-75 are pending. Claims 11-23, 41, 44-48 and 61 have been withdrawn from consideration. Claims 1-10, 24-43, 49-60 and 62-66 stand variously rejected under 35 U.S.C. §§ 112, first paragraph, enablement and second paragraph.

Applicants acknowledge with appreciation that the rejections under 35 U.S.C. § 112, first paragraph, written description and all but one rejection under 35 U.S.C. § 112, second paragraph have been withdrawn. Applicants also gratefully acknowledge that claims 68-73 are in condition for allowance.

Claims 1, 2, 37, 49 and 63 have been amended herein. In particular, claims 1 and 2 now indicates that the expression cassette includes a sequence encoding an immunogenic HIV Gag polypeptide as described throughout the specification, for example on page 14, lines 13-18. Claim 37 has been amended to provide antecedent basis and claim 63 has been amended for clarity. Claim 49 has been amended to recite a method of generating an immune response. No new matter has been added as a result of these amendments and entry thereof is respectfully requested. The amendments are made to expedite prosecution and are not made for reasons related to patentability.

In view of the following remarks and foregoing amendments, Applicants respectfully request reconsideration of the application.

Priority

The Examiner has asked for Applicants to specifically point out if SEQ ID NO:3 and SEQ ID NO:4 are disclosed in 60/114,495. (Office Action, page 2). These two sequences are not set forth precisely in this provisional application. However, other HIV Gag-encoding sequences are described as are general methods of obtaining these and other sequences.

Drawings

Formal drawings are submitted herewith.

35 U.S.C. 112, First Paragraph, Enablement

Claims 1-10, 24-43, 49-60 and 62-66 remain rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. In particular, it is alleged that while the specification is enabling for (1) an expression cassette comprising a polynucleotide

sequence encoding a Gag polypeptide as set forth in (a) SEQ ID NOs:1 or 2 and (b) SEQ ID NOs:3 and 4; (2) the expression cassette of (1)(b) further comprising a sequence encoding an HIV protease polypeptide; (3) the expression cassette of (1)(b) further comprising a polynucleotide sequence encoding an HIV polymerase polypeptide; (4) a composition for generating an immune response in a mammal comprising the expression cassette of (1)(a); (5) a method for generating an immune response in a mammal comprising intramuscularly administering the expression cassette of (1)(a) to the mammal; and (6) a cell comprising the expression cassette of (1)(a), wherein the polynucleotide sequence is operably linked to control elements compatible with expression in the cell, but that it does not reasonably provide enablement for the rest of disclosure. (Office Action, page 3). It is alleged that it would require undue experimentation to make and/or use sequences having at least 90% identity to those presented as SEQ ID NOs:1-4. (Office Action, page 6). In addition, the Examiner cites various references in support of the enablement rejection, alleging that the state of the art in vaccines is unpredictable. (Office Action, pages 3-18).

Applicants traverse the rejections and supporting remarks.

Before addressing each issue raised by the Office, Applicants note the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the Applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

The factors relevant to a determination of enablement are set forth in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The record as a whole is overwhelming clear that the claims are fully enabled by the specification as filed. For the

reasons detailed below, the Office has failed to establish a *prima facie* case of non-enablement with respect to any of the pending claims.

Percent Identity

The Examiner continues to maintain that the as-filed specification does not provide sufficient description for one of skill in the art to make a sequence having at least 90% identity to any of the sequences presented in SEQ ID NOs:1-4. (Office Action, page 6). In particular, it is alleged that the specification does not provide sufficient guidance for what amino acids of any of the sequences listed above may be changed while Gag polypeptide activity is retained. (Office Action, page 14).

Applicants first note that the original claims in no way encompassed non-Gag encoding sequences. Nonetheless, to expedite prosecution, Applicants have amended the claims herein to specify that the sequences encompassed by the claims must (1) exhibit at least 90% sequence identity (at the nucleotide level) to SEQ ID NOs:1-4 and (2) encode a polypeptide including at least one HIV Gag antigen. In other words, the claims require that the expression cassette include a sequence encoding at least one Gag antigen. (See, *e.g.,* Section 2.2.3. starting on page 35 of the specification). Thus, because the claims are directed to expression cassettes including sequences that encode one or more Gag antigens, sequences exhibiting less than 90% nucleotide identity to SEQ ID NOs:1-4 are not encompassed by the claims. Similarly, sequences that do not encode immunogenic Gag antigen(s) are also not encompassed the claims. Rather, the claims encompass only those sequences exhibiting the required identity to SEQ ID NOs:1-4 and which encode at least one Gag antigen. The specification fully enables these claims throughout their scope. As previously noted, the specification details how to determine nucleotide sequence identity and, moreover, amply describes that the Gag polypeptide encoded by these sequences includes a Gag antigen. (See, *e.g.,* Response filed March, 2002).

Further, when Dr. Donnelly analyzed whether the sequences having at least 90% identity to SEQ ID NO:1-4 were enabled, he concluded:

> 5. It is my opinion that, as a technical matter, a skilled worker could have readily made and used the compositions and methods of the pending claims in light of the specification, together with the common general knowledge, tools and methods available in December 1999. I base this opinion on the facts set forth below; however, I call attention to the fact that it was considered routine experimentation at the time of filing to determine a sequence having (i) at least

90% sequence identity to SEQ ID NO:1-4 and (ii) encoding an immunogenic Gag polypeptide; to express such polynucleotides in stem cells or their progenitors; to deliver in a variety of ways such polynucleotides to generate an immune response in a subject. In addition, in drawing my conclusions, I have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the existence of working examples, the direction present in the specification, the state of the field at the time the application was filed and the level of skill in the art. ...

7. In December 1999, the quantity of experimentation required to identify sequences exhibiting 90% identity to SEQ ID NOs:1-4 was quite low. For example, BLAST software programs were commonly known and readily available on the Internet at this time. This set of programs allows for an easy alignment and determination of percent identity as between any sequences. The skilled worker could have easily used the BLAST or any number of other similar programs to determine the percent identity between sequences (in this case between any given sequence and those presented SEQ ID NOs:1-4). The specification also provides extensive guidance in this regard, for example, on page 17, line 3 through page 19. Working examples are also provided, for example comparisons of the claimed sequences to wild-type HIV sequences. (See, Figure 5). Furthermore, the skilled worker could have readily generated any sequence falling within the scope of the claims using routine methods, for example by utilizing PCR to generate sequences, by introducing point mutations and the like. Thus, it is my opinion that it would have required only routine experimentation to determine sequences falling within the 90% identity, as claimed.

8. In addition, the specification provides significant direction for evaluating whether sequences having 90% identity to SEQ ID NO:1-4 encode an immunogenic Gag polypeptide. Those of us working in the field of gene delivery and immunology are well versed in the various tests for determining immunogenicity, which include computer analysis of sequences, comparison to known immunogenic sequences as well as functional tests (*e.g.*, ELISAs, CTL assays and others described in the Examples of the specification). Examples present in the specification demonstrate the generation of sequences and immunogenicity testing of these sequences. (See, Examples 1 and 4).

9. Furthermore, the state of the art in December 1999 was quite sophisticated with regard to determining both sequence identity and evaluating immunogenicity. I have described above some of the tools, programs and methods available in the field of recombinant nucleic acid technology in December 1999 and many other examples of homologous nucleic acid molecules that encode immunogenic proteins were also available. Therefore, it is my opinion that, following the guidance of the specification, a scientist could have readily made and used polynucleotide sequences that exhibit at least 90% sequence identity to SEQ ID NO:1-4 and which encode an immunogenic HIV Gag polypeptide.

10. Preparing polynucleotides encoding immunogenic Gag polypeptides in December 1999 was a predictable art. There is no doubt that a skilled worker

> would have been able to make and use sequences exhibiting 90% identity to SEQ ID NO:1-4 and encoding an immunogenic polypeptide. Even if a rare construct were inoperable for some reason (*e.g.,* it wasn't immunogenic), the skilled worker would have readily modified the construct according to the alternatives available at the time and described in the specification. In other words, to the skilled worker, an inoperable construct would itself be a useful starting material for other operable constructs. Essentially all molecules that fall within the claims would be useful for making or using defining technical features of the claims, *i.e.,* nucleotide sequences having 90% sequence identity to SEQ ID NO:1-4 and which encoded an immunogenic HIV Gag polypeptide.

In sum, when the *Wands* factors are considered, it is clear that the record establishes that the specification as filed fully enables the pending claims throughout their scope. Therefore, Applicants submit that this rejection should be withdrawn.

Claims 62-63

Claims 62 and 63 were also rejected in the Office Action on the grounds that the specification allegedly fails to provide sufficient guidance as to polypeptides "derived" from HIV. Although Applicants disagree that the specification doesn't adequately define the term "derived," claim 63 has been amended herein to eliminate the term. The amendment, which is made solely to expedite prosecution, obviates this rejection.

Methods of Generating an Immune Response

The Examiner also continues to maintain that the claims encompass methods of immunization (or "nucleic acid immunization"). (Office Action, pages 15-16). In support of this rejection, the Examiner points to a definition of "nucleic acid immunization" on page 16 of the specification as well as a dictionary definition of "immunization" in which the response generated must be protective. (Office Action, pages 15-16).

Applicants reiterate that none of the claims are directed specifically toward "immunization" methods *per se* and, accordingly, it is irrelevant how the specification and art define "immunization." Rather, what is relevant is how the specification and art define generating "an immune response." This term is clearly defined in the specification as the development in a subject of a humoral and/or cellular immune response. (See, page 15, lines 15-17 of the specification). In addition, it is clearly indicated that such a response may or may not be protective and/or therapeutic:

> Thus, an immunological response as used herein **may** be one which stimulates the production of CTLs, and/or the production or activation of helper T- cells. The antigen of interest **may** also elicit an antibody-mediated immune response. Hence, an immunological response **may** include one or more of the following effects: the production of antibodies by B-cells; and/or the activation of suppressor T-cells and/or γδ T-cells directed specifically to an antigen or antigens present in the composition or vaccine of interest. These responses **may** serve to neutralize infectivity, and/or mediate antibody-complement, or antibody dependent cell cytotoxicity (ADCC) to provide protection to an immunized host. Such responses can be determined using standard immunoassays and neutralization assays, well known in the art. (page 14, lines 3-12, emphasis added).

Thus, the immune response generated by the claimed expression cassettes may be protective (*e.g.*, immunize a subject) or not protective. Applicants remind the Office that are entitled to be their own lexicographer. Furthermore, Applicants' definition of generating "an immune response" is not repugnant to the art-recognized use of this particular term. In fact, as shown in the attached pages, the Dictionary of Microbiology and Molecular Biology is in accord -- generating an immune response (*e.g.*, any humoral or cellular response) is a broader term than immunization and, accordingly, the claim term includes protective and non-protective responses.

In the case at hand, there is no dispute that Applicants have enabled methods of generating an immunological response in a subject using an expression cassette as claimed. (See, Exhibit A submitted with Response filed March, 2002 and Exhibit B submitted herewith). Because Applicants are not claiming "immunization" methods *per se*, they are under no obligation to establish whether or not the immunological responses generated are partially or wholly protective and/or therapeutic or even what amount of Gag expression is required for such treatment.

Dr. Donnelly concurs:

> 11. Similarly, the specification as filed clearly provides ample guidance on how to generate an immune response (humoral and/or cellular) in a subject by administering the claimed sequences. (See, page 7, lines 9 to 20; page 12, line 28 to page 13, line 15; and Examples 4 and 7). Indeed, in December 1999, it was predictable and routine to evaluate whether an immune response was generated against a polypeptide antigen encoded by an administered polynucleotide, for example using the techniques and tools described above in paragraph 8. Furthermore, the skilled worker would know that generating an immune response does not necessarily mean that the subject will be vaccinated – *i.e.*, protected against HIV infection or derive some therapeutic benefit. The skilled worker would also have known that immune responses are useful for numerous scientific

purposes, such as laboratory assays, preparing reagents for virologic and immunologic studies, analyzing immune responses, and preparation of diagnostic kits. Therefore, a skilled worker would have known that the claimed sequences could be used for additional scientific purposes other than seeking protective immunity or a therapeutic benefit. In view of the guidance in the specification, the predictability and state of the art, and high level of the skilled worker, it is plain that it would have been routine to administer a polynucleotide and evaluate whether or not an immune response to the encoded polypeptide was generated in the subject.

12. Moreover, in the course of further work on HIV, the inventors have evaluated the immune responses generated upon administration of the claimed Gag-encoding polynucleotide constructs to subjects. The manuscript attached hereto (Exhibit B) shows that the claimed expression cassettes generate both humoral and cellular responses when made and administered to animal subjects as described in the specification. (See, for example, Figures of Exhibit B and text describing these Figures). Specifically, this manuscript demonstrates that neutralizing antibodies develop more rapidly in animals vaccinated with the claimed constructs; that these neutralizing antibodies correlated with lower peak viremia after pathogenic virus challenge; and that the claimed Gag-encoding constructs generate cellular immune responses. Thus, although not required by the claims, the claimed constructs are, in fact, able to generate potentially "protective" immune responses. Accordingly, a skilled worker could readily practice the claimed methods of generating an immune response in view of the teachings of the specification and state of the art as filed.

In addition, Dr. Donnelly also provides still further data regarding the ability of the claimed polynucleotide sequences to generate both cellular and humoral immune responses. Exhibit B of Dr. Donnelly's declaration presents data obtained from vaccination studies in primates using the expression cassettes that were made and administered as described in the specification. This manuscript demonstrates that neutralizing antibodies develop more rapidly in animals vaccinated with the claimed constructs and that these neutralizing antibodies correlated with lower peak viremia after pathogenic virus challenge. In addition, the manuscript demonstrates that the claimed constructs generate cellular immune responses.

In sum, Applicants' specification fully enables the use of the claimed expression cassettes to generate an immune responses. Therefore, withdrawal of this rejection is in order.

Cells

It is further maintained that the state of the art and the specification do not provide sufficient guidance for claims encompassing stem cells or progenitor cells thereof comprising an

expression cassette of claim 1. (Office Action, page 10). In support of the rejection, the Examiner states:

> One skilled in the art and considered would understand that if the expression cassette is not stably integrated into the genome of the host cell *e.g.* lymphoid cell, it would not be present after several rounds of replication. Also, one skilled in the art would understand that the development of a successful strategy for long-term gene expression in stem cells is immense [citing Prince et al.]. ... Thus, in view of the specification and state of the art, the specification does not provide sufficient guidance for one skilled in the art to make and use stem cells or progenitor cells with the expression cassette of claim 1. (Office Action, page 10).

Because the specification fully enables the claimed cells, Applicants traverse the rejection. To reiterate, the cells of the present invention must include an expression cassette of claim 1 and be operably linked to a control elements compatible with expression in the cell. The claims do not require that the expression cassettes be stably integrated into the genome of the host cell. Indeed, a lymphoid cell that does not contain an integrated or an extrachromosomal expression cassette as claimed (*e.g.,* due to several rounds of replication) would not fall within the scope of the claims. Moreover, the term "progenitor" refers to a progenitor of one of the listed cells and does not refer exclusively to progeny in which the claimed sequences are necessarily passed down from the parent cell. In other words, the sequences can be introduced directly into the progeny.

The references cited by the Office as allegedly demonstrating difficulties of gene therapy are <u>not</u> addressing introduction of sequences into host cells themselves, but, rather, difficulties associated with reintroduction of transduced cells into a subject. In the pending case, the claims at issue are directed to cells comprising an expression cassette of claim 1, not to methods of administering transduced stem cells to subjects. Furthermore, even the cited references make it clear that heterologous sequences can readily be introduced into and expressed in stem cells:

> Other areas where gene transfer into hematopoietic cells is being investigated include human immunodeficiency virus (HIV) infection ... the importance of these studies cannot be over emphasized as they provide 'proof-in-principle' that gene-marked cells can survive and <u>be expressed</u> for extended periods of time once re-introduced into the host. (Prince, page 340, left column, emphasis added).

Dr. Donnelly also addresses this issue and concludes:

> 13. It would have also been routine to express the claimed Gag-encoding polynucleotides in stem cells or lymphoid progenitor cells. The guidance in the

specification in this regard is extensive. (See, Section 2.3.2 starting on page 61 of the specification). In addition, the level of skill in this field was very high at the time of filing, the state of the art sophisticated and the experimentation needed to get expression in lymphokine cells (such as stem cells and lymphoid progenitor cells) was routine using standard vectors (*e.g.*, plasmids such pBR322 and pBLUESCRIPT that include promoters and other control elements). Even a reference cited in the Office Action makes it clear that heterologous HIV polypeptide-encoding sequences can readily be introduced into and expressed in stem cells:

> Other areas where gene transfer into hematopoietic cells is being investigated include human immunodeficiency virus (HIV) infection ... the importance of these studies cannot be over emphasized as they provide 'proof-in-principle' that gene-marked cells can survive and be expressed for extended periods of time once re-introduced into the host. (Prince, *Pathology* 30:335-347 at page 340, left column, emphasis added).

Therefore, the specification teaches a skilled worker how to express the claimed Gag-encoding sequences in stem cells or progenitors of lymphoid cells.

Thus, the specification fully enables claims directed to cells (*e.g.*, lymphoid cells) comprising an expression cassette of claim 1.

Delivery

In the pending case, the Office acknowledges that the claims are enabled for specific sequences and use of these sequences to generate immunological responses in mammals when administered intramuscularly. (Office Action, page 3). However, the Examiner cites numerous references allegedly showing the unpredictability of nucleic acid vaccines by delivery routes other than intramuscular. (citing Gurunathan, Anderson, Verma, Nathanson, Prince, Azevedo and McCluskie). (Office Action, pages 3-18).

For the reasons previously of record, Applicants again submit that none of the cited references address the specifically claimed compositions or use of these compositions to generate an immune response. (See, also, Response filed March, 2002). Again, these references are all directed to therapies and/or vaccines. In contrast, the pending claims are directed to compositions and methods that generate any kind of immune response. Thus, the references do nothing to establish that methods of eliciting an immune response to the claimed expression cassettes are not enabled by Applicants' specification.

Furthermore, the references do not establish that modes of delivery other than intramuscular would not result in expression of Gag-antigen(s) or in the generation of an immune

response. As noted above, Prince actually states that expression in hematopoietic cells of HIV polypeptides has been shown. In addition, McCluskie is directed entirely to a comparison of routes of administration for vaccination. Indeed, while McCluskie focuses on how various routes of administration produce more or less immunity, a complete reading of this reference fully supports Applicants claims -- virtually all routes of DNA administration (encoding a variety of heterologous sequences) are able to generate some kind of an immune response in the subject to the polypeptide encoded by the heterologous nucleotide sequence. Thus, the references cited by the Office actually provide evidence that the specification fully enables multiple delivery routes of DNA in order to generate an immune response in a subject.

Still further evidence that the specification as filed in view of the state of the art at the time of filing fully enables all routes of delivery is submitted herewith. In this regard, Shiver et al. 1997 *Vaccine* 15:884-887 (Abstract attached hereto) demonstrates that intradermal administration of DNA resulted in immune responses against HIV antigens in rodents and non-primate species. Similarly, Durani et al. 1998 *J. Immunol. Methods* 220:93-103 demonstrates how mucosal (*e.g.*, intranasal and oral) administration of DNA encoding an HIV antigen generates systemic and humoral immune responses. These references demonstrate yet again that the specification as filed fully enables claims encompassing multiple routes of delivery. (See, also paragraph 14 of Dr. Donnelly's Declaration).

In sum, Applicants have provided ample factual evidence which demonstrates that the specification enables the pending claims throughout their scope. This evidence includes (1) textbook teachings and dictionary definitions regarding the art-recognized difference between generating an immune response and immunization as defined in the specification; and (2) various references demonstrating the specification is indeed enabling, for example for multiple routes of delivery. When properly considered, the evidence and facts of record clearly establish that the claims are fully enabled by the specification.

35 U.S.C. § 112, Second Paragraph

Claim 37 is alleged to be indefinite because of improper antecedent basis. (Office Action, page 20). By amendment herein, claim 37 has been corrected as suggested by the Examiner, thereby obviating this amendment.

Provisional Double Patenting

Applicants request the provisional double patenting rejection be held in abeyance until the claims in one of the applications in question provides to issuance.

Information Disclosure Statement

Applicants wish to bring to the attention of the Patent Office the references listed on the attached PTO-1449 form and request that they be considered by the Examiner. Copies of the references cited on the attached are enclosed herewith (six boxes). The information listed on the attached PTO-1449 forms may be material to the examination of the above-identified application. The Examiner is respectfully requested to make this information of official record in the application.

This Information Disclosure Statement under 37 CFR §1.97 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

This information disclosure statement is being filed under 37 C.F.R. §1.97(c)(2), therefore, enclosed is a check to cover the $180 fee due under 37 C.F.R. §1.17(p). The Commissioner is hereby authorized to charge any additional fees and to credit any overpayment of fees, which may be required under 37 C.F.R. §1.16 and §1.17, or §1.21, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2302-1631.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2302-1631.

Please direct all further communications regarding this application to:

Anne S. Dollard, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2719
Facsimile: (510) 655-3542.

Respectfully submitted,

Date: 12/17/02

By: _____

Roberta Robins
Attorney for Applicants
Registration No. 33,208

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 1, 2, 37, 49 and 63, as indicated below:

1. (Twice Amended) An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an immunogenic HIV *Gag* polypeptide, wherein the polynucleotide sequence encoding said *Gag* polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented as either nucleotides 844-903 of Figure 1 (SEQ ID NO:1) or nucleotides 841-900 of Figure 2 (SEQ ID NO:2).

2. (Twice Amended) An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an immunogenic HIV *Gag* polypeptide, wherein the polynucleotide sequence encoding said *Gag* polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented as Figure 1 (SEQ ID NO:3) or Figure 2 (SEQ ID NO:4).

37. (Amended) The cell of claim 36, wherein the antigen presenting cell is a lymphoid cell is selected from the group consisting of macrophage, monocytes, dendritic cells, B-cells, T-cells, stem cells, and progenitor cells thereof.

49. (Twice Amended) A method of [immunization of] generating an immune response in a subject, comprising,

introducing the composition of claim 41 into said subject under conditions that are compatible with expression of said expression cassette in said subject.

63. (Twice Amended) The method of claim 62, where the method further comprises administration of [a] an HIV polypeptide[derived from an HIV].